

정신분열병 환자에서 Ziprasidone의 유지치료 효과

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ABSTRACT

Efficacy of Ziprasidone in Maintenance Treatment of Patients with Schizophrenia

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Schizophrenia is a chronic disorder which needs maintenance treatment. The authors reviewed available studies focusing on reduction of the rate of relapse and maintenance of symptom control in long-term clinical trials of ziprasidone. Placebo controlled study demonstrated that long-term treatment with ziprasidone could reduce the risk of relapse and maintain the control of symptoms, especially negative symptoms. Ziprasidone showed comparable efficacy with haloperidol, olanzapine, and risperidone in terms of relapse prevention and maintenance of symptom control in long-term clinical trials. (Korean J Psychopharmacol 2005;16(Supplement 3):20-27)

KEY WORDS : Ziprasidone · Relapse · Long term efficacy · Maintenance treatment.

서 론

정신분열병은 만성 질환으로 지속적인 유지치료가 필요하다. 저자들은 정신분열병 환자에 대한 장기 임상시험에서 ziprasidone의 유지치료 효과에 대해 검토하였다. Placebo controlled study에서 ziprasidone의 장기 치료는 relapse 위험을 감소시키고 증상 조절을 유지할 수 있음을 보여주었다. 특히 음성 증상(negative symptom)의 조절에 효과적이었다. Ziprasidone은 haloperidol, olanzapine, risperidone과 relapse 예방 및 증상 조절의 측면에서 장기 임상시험에서 비교 가능한 효과를 보였다. (Korean J Psychopharmacol 2005;16(Supplement 3):20-27)

키워드 : Ziprasidone · Relapse · Long term efficacy · Maintenance treatment.

. Leucht ⁶⁾

가, 2

가, 2

clozapine

olanzapine

(compliance)

(tolerability)

(efficacy)

가

Ziprasidone 2001 3

2004 4 가

2005

ziprasidone

ziprasidone 5-HT₂/D₂

(antagonist), 5-HT_{1A}

(partial agonist) serotonin norepinephrine (reuptake) ⁷⁾ 5-HT₂

5-HT_{1A}

(prefrontal cortex) dopamine

가 ⁸⁾ ziprasidone

가 ⁹⁻¹¹⁾

9)

¹¹⁾

ziprasidone 가

ziprasidone

ziprasidone

본 론

1. Ziprasidone과 위약 비교

1) Ziprasidone Extended Use in Schizophrenia [ZEUS] 연구

Arato ¹²⁾ 1, (randomized), (double blind),

ziprasidone, 40 mg/day, 80 mg/day, 160 mg/day (fixed dose)

2 CGI-S 5 (markedly ill), Positive and Negative Syndrome Scale (PANSS) P7(hostility) G8(uncooperativeness) 5 (moderate severe)

PANSS, Global Assessment of Functioning(GAF) scale, Clinical Global Impressions(CGI) scale

가 (baseline)

(PANSS 16.7 - 18.0)

(PANSS 24.8~25.8)

(GAF 46.9~48.0) Clinical Global Impressions - Improvement(CGI-I) 가 6 (much worse)

PANSS P7 (hostility)

G8 (uncooperativeness) 6 (severe)

2

ziprasidone

ziprasidone 40 mg 38%(27), 80 mg 31%(21), 160 mg 34%(23), 61%(43) ziprasidone (ziprasidone 40

mg/day, 80 mg/day, 160 mg/day p<0.01, p<0.001, p<0.01,). 6

6, ziprasidone 9%(10/110), 42%(8/19)

ziprasidone (p=

Ziprasidone

0.001). Kaplan - Meier 1
 , ziprasidone 40 mg
 43%, 80 mg 35%, 160 mg 36%,
 77% ziprasidone
 (ziprasidone 40 mg, 80 mg, 160 mg
 p=0.002, p<0.001, p<0.001,).

(Intention - to - treat last
 observation carried forward, ITT LOCF)

ziprasidone 3 가
 가 (1). PANSS , PA-
 NSS , CGI - S, GAF 가
 ziprasidone
 PANSS
 6 , 16
 가
 가 , ziprasidone 3 PANSS
 가

2) ZEUS 연구의 경로 분석(path analysis)

ZEUS ziprasidone PA-
 NSS negative subscale 가
 Meltzer ¹³⁾ ziprasidone . PA-
 NSS 1
 2
 ziprasidone 1
 44% (p=0.017) . ZEUS -
 ziprasidone
 160 mg 1 50%
 가
 POCF ziprasidone
 16 1

Table 1. ZEUS 연구에서 약물 효과 변수(ITT LOCF)의 변화¹²⁾

	Treatment		Baseline (Mean ± SD)	Endpoint (Mean ± SD)	Mean Change	P ^a
	Dosage (mg/d)	N				
PANSS Total	P	71	88.4 ± 10.0	104.0 ± 27.1	15.6	-
	Z 40 mg/day	71	84.2 ± 18.4	87.1 ± 27.6	2.9	0.001
	Z 80 mg/day	68	86.2 ± 18.6	88.0 ± 30.8	1.9	0.001
	Z 160 mg/day	67	84.5 ± 18.3	83.2 ± 25.8	- 1.3	<0.001
PANSS Negative subscale	P	71	25.3 ± 5.1	27.1 ± 7.2	1.4	-
	Z 40 mg/day	71	24.8 ± 6.3	22.9 ± 7.4	- 1.9	<0.001
	Z 80 mg/day	68	24.8 ± 5.4	23.7 ± 7.4	- 1.0	0.011
	Z 160 mg/day	67	25.1 ± 5.9	22.3 ± 7.0	- 2.8	<0.001
PANSS Positive subscale	P	71	18.0 ± 6.2	24.2 ± 9.0	6.2	-
	Z 40 mg/day	71	17.3 ± 5.7	20.3 ± 9.0	3.0	0.008
	Z 80 mg/day	68	17.9 ± 5.8	19.0 ± 9.0	1.2	<0.001
	Z 160 mg/day	67	16.7 ± 5.4	18.5 ± 8.5	1.8	0.001
CGI-S	P	71	4.1 ± 0.8	5.0 ± 1.2	1.0	-
	Z 40 mg/day	71	4.0 ± 0.7	4.5 ± 1.3	0.4	0.002
	Z 80 mg/day	68	4.0 ± 0.6	4.2 ± 1.4	0.2	<0.001
	Z 160 mg/day	67	4.0 ± 0.7	4.2 ± 1.4	0.1	<0.001
GAF	P	70	46.9 ± 12.8	36.7 ± 15.1	- 10.2	-
	Z 40 mg/day	71	48.0 ± 11.7	44.0 ± 18.7	- 4.0	0.005
	Z 80 mg/day	68	46.9 ± 12.0	45.9 ± 19.6	- 1.0	0.001
	Z 160 mg/day	66	47.6 ± 11.8	46.7 ± 19.6	- 0.9	<0.001

^aP versus for change from baseline (ANCOVA)

3) ZEUS연구를 Penultimate Observation Carried Forward(POCF) 방법으로 분석

O Connor ¹⁴⁾ ZEUS POCF
LOCF 가

, POCF

, LOCF

, POCF

가

. LOCF

가

가

PANSS

zipra-

(1). POCF

ziprasidone

PANSS

가

ziprasidone

(1).

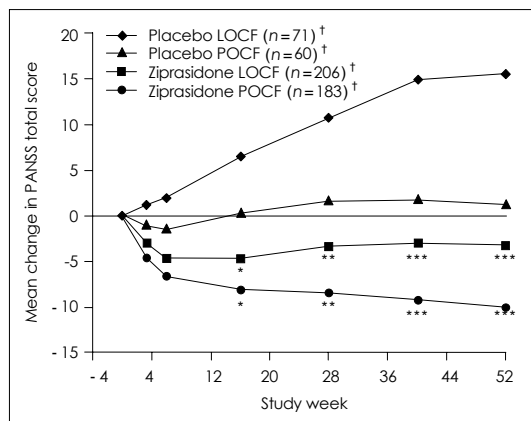


Figure 1. LOCF POCF 방법을 이용한 ZEUS 연구에서 PANSS 전체 점수의 변화 분석.¹⁴⁾ Mean baseline PANSS total scores were as follows : LOCF : placebo=88.44, ziprasidone=84.92, POCF : placebo=88.25, ziprasidone=84.62, † : 2 post-baseline assessments were required for inclusion in POCF analysis. * : p<0.05 vs. placebo, ** : p<0.01 vs. placebo, *** : p≤0.001 vs. placebo.

PANSS

2

. POCF

ziprasidone

2. Ziprasidone과 haloperidol 비교

Hirsch ¹⁵⁾ 28 , ,

zip-

rasidone haloperidol

PANSS P7 G8 5

PANSS

ziprasidone 72.9,

haloperidol 74.4

가

. ziprasidone (N=148)

80 mg/day,

120 mg/day,

160 mg/day

80~160 mg/day

. Haloperidol (N=153)

5

mg/day, 10 mg/day,

15

mg/day

5~15 mg/day

PANSS, Montgo-

gomery - Asberg Depression Rating Scale(MADRS),

CGI - S

가 . 2

(evaluable patients)

가

가

(evaluable patients.

LOCF). ziprasidone 66 (45%) 가, halo-

peridol 64 (42%)

가 28

ziprasidone haloperidol

116.5 mg/day, 8.6 mg/day

Hirsch

(lack of efficacy, insufficient clinical response)

ziprasidone haloperidol

18% (ziprasidone 20/110, haloperidol 21/117)

ziprasidone haloperidol

PANSS

, BPRS core items(the sum of items P2, P3, P6, and G9), MADRS

Ziprasidone

Table 2. 기준시점과 연구종료 시 정신병리의 변화¹⁵⁾

Scale	Ziprasidone		Haloperidol	
	Baseline	Week 28	Baseline	Week 28
PANSS total	73.5 ± 17.4	64.4 ± 22.0	73.7 ± 15.9	68.6 ± 18.8
PANSS negative subscale	22.6 ± 6.4	19.9 ± 7.5	22.6 ± 5.2	19.6 ± 6.0
BPRSd core items	9.6 ± 3.7	8.1 ± 4.0	9.7 ± 3.6	8.4 ± 3.7
CGI-S	4.2 ± 0.8	3.7 ± 1.2	4.2 ± 0.7	3.8 ± 1.1
MADRS	15.0 ± 8.3	13.4 ± 9.3	14.1 ± 7.9	13.5 ± 7.9
GAF	53.0 ± 10.5	56.2 ± 16.2	53.6 ± 9.2	56.1 ± 13.7

(2). PANSS , 1

6

65 . PANSS .¹⁶⁾

60 (remission)

, ziprasidone 62%, haloperidol , ziprasidone (rispe-

55% 가 ridone olanzapine)

. PANSS 20% .

가 ,

(negative symptom

responder) . ziprasidone haloperidol

PANSS

(ziprasidone -3.6, haloperidol -3.0),

ziprasidone haloperidol

(ziprasidone 48% halo-

peridol 33%, p<0.05).

ziprasidone haloperidol

가

negative symptom responder

haloperidol

(potential advantage)

ziprasidone

, ZEUS

ziprasidone 1

160 mg/day

ziprasidone 1

가 , ,

2

3. Ziprasidone과 다른 비정형 항정신병약물과의 비교

1) Olanzapine과의 비교

(1) 6 (continuation study)

Simpson¹⁷⁾ ziprasidone olanzapine

6 (continuation study)

가 6 , ,

(PANSS

20% CGI-I 가 2 [much im-

proved])

6 ziprasidone(N=62)

40 mg, 60 mg 80 mg b.i.d., olanzapine

(N=71) 5 mg, 10 mg 15 mg q.d.

(flexible dose) . ziprasidone

137.2 mg/day olanzapine

12.2 mg/day . BPRS, CGI, PANSS Calgary

Depression Scale for Schizophrenia(CDSS)

가 .

가 (ziprasidone

69.4%, olanzapine 70.4%),

(ziprasidone 62.9%, olanza-

pine 62.0%) 6 160 mg/day)
 PANSS 20% 가
 CGI - S 3 (mildly ill)
 (treatment failure) ziprasidone
 3.2%(2/62), olanzapine 2.8%(2/71)
 . Kaplan - meier
 6 (response main-
 tenance)
 가 ,
 2가
 (logn - term treatment
 effects) 가 6
 (response maintenance)
 가 6
 . ziprasidone olanzapine
 6 6
 BPRS(ziprasidone - 18.1 olan-
 zapine - 19.7, p=not - significant), CGI - S(ziprasi-
 done - 1.8 olanzapine - 1.9, p=not - signifi-
 cant), PANSS (ziprasidone - 32 olan-
 zapine - 33.9, p=not - significant)
 .
 PANSS (ziprasidone - 7.7 olan-
 zapine - 8.0, p=not - significant) PANSS
 (ziprasidone - 9.2 olanzapine - 10.0,
 p=not - significant)
 . ziprasidone olanzapine CDSS
 (ziprasidone
 - 2.0, olanzapine - 2.9).

(2) 28
 Kane ¹⁸⁾ olanzapine ziprasidone
 28 , . BPRS
 42 , PANSS 가
 4 (moderate) CGI - S 4 (mode-
 rately ill)
 .
 olanzapine (N=
 277) ziprasidone (N=271)
 . Olanzapine(10~20 mg/day) ziprasidone(80~

olanzapine 15.1 mg, ziprasidone 114.8
 mg . PANSS, BPRS, CGI - S, CGI - I
 가 .
 PANSS 가 20%
 가 CGI - S가 3
 .
 olanzapine
 (7.2%) ziprasidone (13.7%)
 (p=0.017). 8 PANSS
 가 30%
 olanzapine (58.6%) ziprasidone (42.5%)
 (p<0.001). Kaplan - Meier
 olanzapine (81.6%) ziprasidone
 (62.8%) 가
 (p=0.004).
 olanzapine ziprasidone BPRS total
 (- 21.0 - 15.8, p<0.001), BPRS positive(- 6.8
 - 4.9, p<0.001), BPRS negative(- 3.4 - 2.9, p=
 0.007), BPRS anxiety/depression(- 3.9 - 3.0, p=
 0.001), CGI - S(- 1.6 - 1.1, p<0.001), CGI - I
 (p=0.006), PANSS (p<0.001),
 (p<0.001), (p=0.003), general psy-
 chopathology(p<0.001) cognitive subscale(p<0.001)
 . 가 ziprasidone
 가

2) risperidone과의 비교

Addington ¹⁹⁾ 8 44
 ziprasidone risperidone
 . 8 (PANSS
 가 20% CGI - I 가 2
)
 . ziprasidone 149 62
 가, risperidone 147 77 가
 . ziprasidone 40 mg, 60 mg,

Ziprasidone

80 mg b.i.d.

114 mg/day . risperidone
3 mg, 4 mg, 5 mg b.i.d.
7 mg/day ziprasidone 21
(33.9%), risperidone 32 (41.6%) 가
44

(Insufficient clinical response)
가 ziprasidone risperidone
25.8%, 19.5%
. ziprasidone risperidone 8
44 PANSS
(- 26.66 - 32.43, p=not - significant), PANSS
(- 7.53 - 7.52, p=not - significant),
BPRSd total(- 14.25 - 18.56, p=not - significant),
BPRSd core items(- 5.44 - 6.97, p=not - significant),
CGI - S(- 1.14 - 1.51, p=not - significant),
MADRS(- 5.43 - 4.63, p=not - significant)
(p<0.001)

3) olanzapine 및 risperidone과의 비교의 의의

ziprasidone
(risperidone olanzapine)
가 가
ziprasidone risperidone olanzapine

factory clinical response)

(satis-
factory clinical response)
,
20)
, ziprasidone
(80~160 mg/day) risperidone
(3~5 mg b.i.d) olanzapine(5~15 mg/day)
20)

Simpson ziprasidone olan-
zapine 28 가 Kane ziprasidone

. Kane Simpson

1 forced titration(ziprasidone
: 2 40 mg b.i.d. 5 80 mg b.i.d.
, olanzapine : 2 5 mg q.d.
5 10 mg q.d) olanzapine
(dose ceiling) 15 mg/day olanzapine
가
. Kane Olanzapine bottom dose
ceiling dose 10~20 mg/day ziprasidone
80~160 mg/day
. ziprasidone titration sche-
dule 3 20 mg b.i.d. visit
40 mg b.i.d. visit

. Kane olan-
zapine ziprasidone . Simpson

Kane 가
titration schedule
가 . Simpson
ziprasidone olanzapine
137.2 mg/day 12.2 mg/day , Kane
114.8 mg/day 15.1 mg/day
. ziprasidone olanzapine
titration sche-

dule 가 가 .

결론

10% 가

ziprasidone

ziprasidone, haloperidol, risperidone, olanzapine, ziprasidone

가 ziprasidone 가

중심 단어 : Ziprasidone

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